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RESEARCH ARTICLE

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A novel online prognostic tool to predict long-term survival after liver resection for intrahepatic cholangiocarcinoma: The "metro-ticket" paradigm

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Abstract

Background: The aim of the current study was to develop an online calculator to predict survival after liver resection for intrahepatic cholangiocarcinoma (ICC) based on the "metro-ticket" paradigm.

Methods: Between 1990 and 2016, patients who underwent liver resection for ICC were identified in an international multi-institutional database. The final multivariable model of survival was used to develop an online prognostic calculator of survival.

Results: Among 643 patients, actual 5-year overall survival (OS) after resection for ICC was 42.7%. On multivariable analysis, CA19-9 > 200 (hazard ratio (HR), 2.62; 95% CI, 2.01-3.42), sum of the number and largest tumor size >7 (HR, 1.88; 95% CI, 1.46-2.42), N1 disease (HR, 2.87; 95% CI, 1.98-4.16), R1 resection (HR, 1.72; 95% CI, 1.21-2.46), poor/undifferentiated tumor grade (HR, 1.74; 95% CI, 1.25-2.44), major vascular invasion (HR, 1.47; 95% CI, 1.03-2.10), and adjuvant chemotherapy (HR, 0.64; 95% CI, 0.45-0.89) were significantly associated with survival and were included in the online calculator. The predictive accuracy of the model was good to very good as the C-statistics to predict 5-year OS was 0.696 in the training dataset and 0.672 with bootstrapping resamples (n = 5000) in the test dataset.

Conclusion: A novel, online calculator was developed to estimate the 5-year survival probability for patients undergoing resection for ICC. This tool could help provide useful information to guide treatment decision-making and inform conversations about prognosis.

KEYWORDS
Intrahepatic cholangiocarcinoma, metro-ticket, online calculator, prognosis

1 | INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after hepatocellular carcinoma (HCC). The incidence of ICC has been increasing in the United States and worldwide

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over the last three decades.[1,2] Although surgery remains the best chance for long-term survival among patients with ICC, only 30%-40% of patients present with resectable disease at the time of diagnosis.[3] In addition, even after curative-intent resection, prognosis remains poor with 5-year overall survival (OS) ranging from 15%-40%.[3] Long-term outcomes following surgical resection vary and depend on a wide variety of factors. In turn, several prognostic schemes have been proposed to help both physicians and patients define the relative benefit of surgical resection, as well as estimate life expectancy following surgery.[4,5]

Although current established staging systems, such as the American Joint Committee on Cancer (AJCC) staging system are helpful,[6] these schemas are more applicable to a population of patients. In particular, staging systems typically provide estimates of aggregate survival data for a group of patients who have comparable pathological characteristics.[6] More recently, there has been an increased focus on using specific patient- and tumor-level characteristics to provide individualized survival estimates. To this end, various groups have advocated for nomograms as a means to integrate individual-level variables into a statistical model to predict outcomes.[7-10] The applicability and clinical utility of nomograms are frequently limited, however, due to their cumbersome nature, as well as the inability to easily and readily use nomograms in a simple, real-world clinical setting. In addition, nomograms typically fail to provide clear information on a range of survival estimates as clinical and pathological factors vary.

More recently, several groups have proposed a "metro-ticket" approach to estimate survival. First proposed by Mazzaferro et al,[11] the "metro-ticket" system was based on the concept that the "cost" (ie, worse survival) was higher the "longer you go" (ie, expanded indications for surgery). The initial metro-ticket scheme predicted survival after liver transplantation among patients with HCC that exceeded the Milan criteria.[11] More recently, an updated HCC metro-ticket system incorporated individual tumor characteristics (ie, tumor size and number) and alpha-fetoprotein (AFP) levels.[12] While the metro-ticket approach has been applied to other malignancies such as colorectal liver metastases (CRLM) and gastric cancer,[13,14] its applicability to ICC has never been investigated. As such, the objective of the current study was to apply the principles of the metro-ticket paradigm to patients undergoing liver resection for ICC. Specifically, we sought to develop a novel, easy-to-use online calculator to predict OS following resection of ICC based on a metro-ticket approach that incorporated tumor characteristics, tumor markers, as well as histopathologic findings.

2 | METHODS

2.1 | Study population and data collection

Patients undergoing surgical resection for ICC between January 1990 and December 2016 were identified in a multi-institutional database incorporating data from 15 tertiary institutions (The Ohio State University Comprehensive Cancer Center, Columbus, OH; Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VS; Winship Cancer Institute, Emory University, Atlanta, GA; Fundeni Clinical Institute, Bucharest, Romania; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; Beaujon Hospital, Clichy, France; Erasmus University Medical Center, Rotterdam, The Netherlands; University of Ottawa, Ontario, Canada; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Yokohama City University School of Medicine, Yokohama, Japan; and Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia). For the purpose of this study, only patients with histologically confirmed ICC who underwent curative-intent liver resection without extrahepatic metastasis were included. Patients with macroscopic positive surgical margins (R2 resection) were excluded, as well as patients who had missing data that were required for the development of the prognostic model. The Institutional Review Board of all the participating institutions approved this study.

Patient demographics and clinicopathologic data were extracted including age, sex, race, American Society of Anesthesiologist class, the presence of cirrhosis, preoperative serum level of carbohydrate antigen (CA) 19-9, type of resection, number of ICC, tumor size, lymph nodal status, location of lymph node metastasis, morphological type (MF, mass-forming; IG, intraductal growth; and PI, periductal infiltrating), tumor grade and margin status, major or minor vascular invasion, and the presence of perioperative chemotherapy. Major hepatectomy was defined as the resection of three or more Couinaud segments.[15] Major vascular invasion was defined as invasion of the first- and second-order branches of the portal vein or hepatic arteries, or as an invasion of one or more of the three hepatic veins. In contrast, the microvascular invasion was defined as intraparenchymal vascular involvement identified on histological examination.[6]

2.2 | Statistical analysis

Continuous and categorical variables were presented as medians (interquartile ranges [IQRs]) and frequency (%), respectively. OS was defined as the time interval between the date of surgery and date of death, while time was censored at the date of the last follow-up for living patients. Survival curves were estimated using the Kaplan-Meier method and differences between curves were investigated with the logrank test. The association of clinicopathologic variables with OS was evaluated by using a Cox proportional hazards model. The final model was described using the hazard ratio (HR) and 95% confidence interval (CI).

2.3 | Development and validation of the prognostic model and online application

The final multivariable model was used to develop the prognostic model and the online application. To assess the predictive ability of the final model, the c-index for time-to-event data was calculated with the bootstrapping resample method (n = 5000) using the R

CRAN package Hmisc.[16] C-index is an extension of the area under the receiver operating characteristic curve to survival analysis and was measured as a continuous value ranging from 0.5 (random prediction not different than chance) to 1 (perfect prediction).[17] The c-index results as the probability that, given two randomly selected patients, the patient who died first had a higher probability of death based on the predictive model.[18] The "shiny: Web Application Framework for R" package was used to develop a web application: (https://metroticketicc.shinyapps.io/metroticket_ICC/). For statistical analysis, the STATA software (Stata Corporation, 2011, MP-Parallel Edition) and R CRAN software (v. 3.5.3, 2019) with the packages survival, shiny, and Hmisc were used.

3 | RESULTS

3.1 | Patient characteristics

Among 1154 patients who underwent hepatectomy for ICC between 1990 and 2016, a total of 643 patients met inclusion criteria and were included in the analytic cohort. Median patient age at the time of surgery was 59 years (IQR, 50-68) and more than half of the patients were male (n = 382, 59.4%). The majority of patients were non-Caucasian, non-African American (n = 421, 65.5%) and did not have cirrhosis (n = 555, 86.3%). Roughly half of the patients underwent major hepatectomy (n = 323, 50.4%) and most patients had the unilobar disease (n = 549, 85.6%). The median tumor number and largest tumor size were 1 (IQR, 1-1) and 5.7 cm (IQR, 4.0-8.0), respectively, resulting in a median sum of 7.0 (5.0-9.5). Median preoperative CA19-9 levels were 45.8 UI/mL (IQR, 18.0-192.7; Table 1). Most patients had an R0 resection (n = 572, 89.2%), MF or IG morphologic ICC type (n = 565, 91.3%), and well to moderately differentiated tumors (n = 541, 86.1%); only a small subset had major vascular invasion (n = 72, 11.2%). On histology, the microvascular invasion was present in 27.3% (n = 175) of patients. A minority of individuals received adjuvant (n = 131, 20.6%) and neoadjuvant chemotherapy (n = 43, 6.8%).

3.2 | Clinicopathological factors associated with OS

After a median follow-up of 21.2 months (IQR, 11.2-38.9), OS after liver resection for ICC was 80.3%, 54.3%, and 42.7% at 1, 3, and 5 years, respectively. On multivariable analysis, after controlling for competing factors, preoperative CA19-9 > 200 (HR, 2.62; 95% CI, 2.01-3.42) and the sum of lesion number and largest tumor size >7 (HR, 1.88; 95% CI, 1.46-2.42) were associated with higher hazards of death. Perhaps not surprisingly, N1 (HR, 2.87; 95% CI, 1.98-4.16) and Nx status (HR, 1.68; 95% CI, 1.20-2.35), R1 resection (HR, 1.72; 95% CI, 1.21-2.46), poor/undifferentiated tumor grade (HR, 1.74; 95% CI, 1.25-2.44), and major vascular invasion (HR, 1.47; 95% CI, 1.03-2.10) were also associated with poor OS. In contrast, receipt of adjuvant chemotherapy was associated with 35% decreased hazards of death (HR, 0.65; 95% CI, 0.45-0.89; Table 2).

TABLE 1 Demographic and patient characteristics in the entire cohort

Variable	N (%)
Age, median (IQR)	59 (50-68)
Male	382 (59.4%)
Race	
Caucasian	206 (32%)
African American	16 (2.5%)
Other	421 (65.5%)
Cirrhosis	88 (13.7%)
CA19-9, UI/mL; median (IQR)	45.8 (18.0-192.7)
Neoadjuvant therapy	
No	588 (93.2%)
Yes	43 (6.8%)
Type of resection	
Minor resection	318 (49.6%)
Major resection	323 (50.4%)
Location	
Unilobar	549 (85.6%)
Bilobar	92 (14.4%)
Number of tumor nodule, median (IQR)	1 (1-1)
Tumor size, cm; median (IQR)	5.7 (4.0-8.0)
Sum of the number and largest size of the tumor	7.0 (5.0-9.5)
Lymph node metastasis	
Nx	349 (54.3%)
N0	183 (28.5%)
N1	111 (17.3%)
Margin status	
R0	572 (89.2%)
R1	69 (10.8%)
Morphologic type	
MF, IG	565 (91.3%)
PI, MF+PI	54 (8.7%)
Grade	
Well to moderate	541 (86.1%)
Poor to undifferentiated	87 (13.9%)
Major vascular invasion	
No	570 (88.7%)
Yes	72 (11.2%)
Microvascular invasion	
No	466 (72.7%)
Yes	175 (27.3%)
Adjuvant chemotherapy	
No	505 (79.4%)
Yes	131 (20.6%)

Abbreviations: CA, carbohydrate antigen; IG, intraductal growth; IQR, interquartile range; MF, mass-forming; PI, periductal infiltrating.

TABLE 2 Cox regression analysis of clinicopathological factors associated with survival

	Bivariate analysis		Multivariable analysis	
Variable	**HR**	**95% CI**	**HR**	**95% CI**
Cirrhosis				
No	Ref		Ref	
Yes	1.02	0.74-1.41	1.27	0.90-1.80
CA19-9, UI/mL				
≤200	Ref		Ref	
>200	2.60	2.04-3.31	2.62	2.01-3.42
Type of resection				
Minor	Ref		Ref	
Major	1.31	1.04-1.65	0.91	0.67-1.24
Number summed to size of tumor nodule				
≤7	Ref		Ref	
>7	1.90	1.49-2.40	1.88	1.46-2.42
Lymph node status				
N0	Ref		Ref	
Nx	1.33	0.99-1.79	1.68	1.20-2.35
N1	2.78	1.96-3.94	2.87	1.98-4.16
Margin status				
R0	Ref		Ref	
R1	1.90	1.37-2.64	1.72	1.21-2.46
Grade				
Well to moderate	Ref		Ref	
Poor to undifferentiated	1.74	1.29-2.37	1.74	1.25-2.44
Major vascular invasion				
No	Ref		Ref	
Yes	1.68	1.21-2.33	1.47	1.03-2.10
Microvascular invasion				
No	Ref		Ref	
Yes	1.36	1.05-1.75	1.06	0.78-1.43
Adjuvant chemotherapy				
No	Ref		Ref	
Yes	0.93	0.70-1.25	0.65	0.45-0.89

Abbreviations: CA, carbohydrate antigen; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

3.3 | Predicting 5-year OS using the online calculator

The online model to predict 5-year OS among patients undergoing resection for ICC is available at https://metroticket-icc.shinyapps.io/metroticket_ICC/. Number and largest size of the tumor, preoperative CA19-9 levels, lymph node status, margin status, and grade of tumor differentiation were included in the online model as "principal characteristics" (Figure 1A). Moreover, type of resection, presence of cirrhosis, major and microscopic vascular invasion, as well as receipt of adjuvant chemotherapy were also included in the model as "additional information" (Figure 1B). On the basis of the model, a range of survival outcomes could be estimated following resection of ICC. For example, a patient with a preoperative CA19-9 of 200.0 UI/mL who underwent a resection of a 5 cm, solitary, well-differentiated ICC and had negative surgical margins, negative lymph nodes, no evidence of major or microscopic vascular invasion, and no receipt of adjuvant treatment after resection had an estimated 5-year OS of 55% (Figure 1C). In contrast, a patient with a preoperative CA19-9 of 400.0 UI/mL who underwent a resection of a 7 cm, solitary, moderate-differentiated ICC and had negative surgical margins, metastatic lymph nodes, no evidence of microscopic, and major vascular invasion, the presence of cirrhosis who received adjuvant treatment after major resection would have an estimated 5-year OS of 21% (Figure 1D).

3.4 | Predictive performance of the model

To assess the predictive accuracy of the online calculator, patients were categorized into different subgroups based on the xpredicted 5-year OS: class I, >75%; class II, 51-75%; class III, 26-50%; and class IV, <25%. In turn, the actual 5-year OS was evaluated among the different subgroups: class I, 70.5% (95% CI, 47.0-100%); class II, 59.0% (95% CI, 51.0-68.2%); class III, 40.8% (95% CI, 32.6-51.1%), and class IV, 12.9% (95% CI, 7.1-23.2%; Figure 2). Of note, the predictive accuracy (discrimination) of the final model was good to very good as the model C-statistic to predict 5-year OS was 0.696 in the training dataset and 0.672 with bootstrapping resamples (n = 5000) in the test dataset.

4 | DISCUSSION

While ICC is an aggressive tumor with generally poor prognosis following surgical resection, the long-term prognosis can vary significantly.[2,19-21] Accurate prognostication of long-term survival remains important for clinicians to guide treatment decision-making, as well as for patients to understand their prognosis. To date, several prognostic models and nomograms have been developed to determine the prognosis of patients undergoing surgery for hepato-pancreato-biliary malignancies.[22-25] In comparison with the traditional AJCC staging system, these nomograms are thought to tailor prognostication based on the individual patient characteristics and clinicopathological factors, and, thus, have been proposed for a number of cancers.[10,26-30] Nevertheless, the clinical applicability of nomograms is limited due to the lack of a simple calculator available for use among clinicians. In addition, many nomograms have suffered from modest-to-poor prognostic discrimination.[4] The current study was important because we developed a novel, easy-to-use, online calculator based on the "metro-ticket" paradigm to predict 5-year OS among patients undergoing surgery for ICC. Of note, factors such as CA19-9 > 200, the sum of the number and largest size of tumor >7, metastatic lymph nodes, R1 resection, poor/undifferentiated tumor grade, and presence of vascular invasion and adjuvant chemotherapy were adversely associated with OS. In contrast, only the receipt of

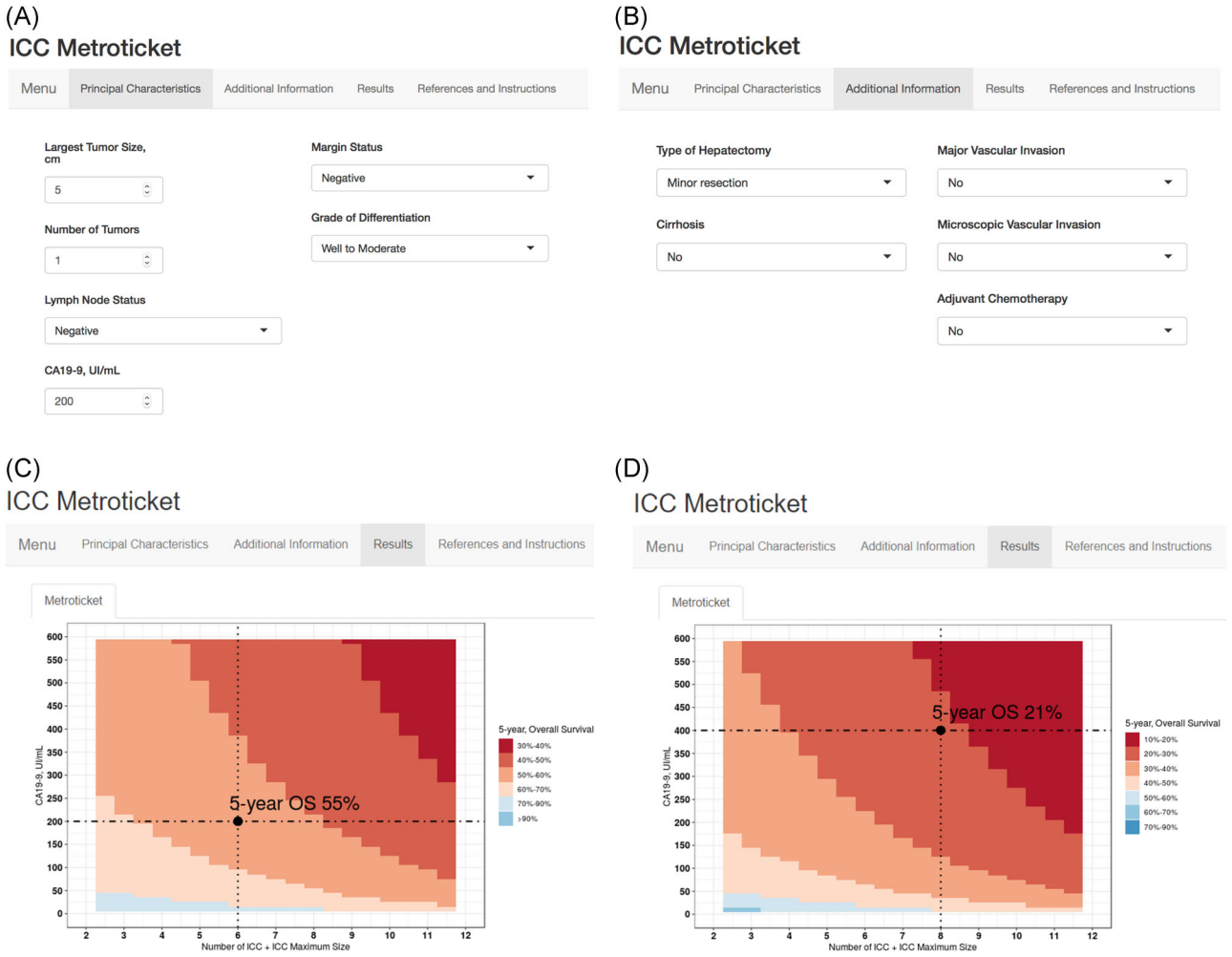

FIGURE 1 Illustration of the online calculator with principal characteristics (A), additional information (B), and the resultant predicted 5-year OS (C, D). ICC, intrahepatic cholangiocarcinoma; OS, overall survival [Color figure can be viewed at wileyonlinelibrary.com]

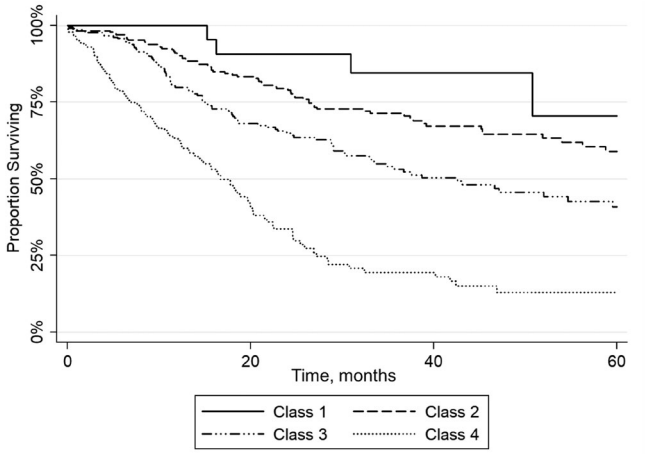

FIGURE 2 Kaplan-Meier curve showing the actual OS of patients stratified by classes of predicted OS. OS, overall survival

adjuvant chemotherapy was associated with decreased hazards of death. By combining the aforementioned variables, along with cirrhosis—an established prognostic factor for ICC,[31-33] we developed an online calculator that predicted 5-year OS among patients undergoing resection for ICC. The model showed a good predictive ability in the training (C-statistic = 0.696) and validation cohorts (C-statistic = 0.672). Perhaps of more interest, when patients were categorized in different groups based on their predictive 5-year OS, actual OS was similar to OS predicted by the model. To the best of our knowledge, this is the first study to provide a simple, easy-to-use online calculator to estimate the 5-year OS probability among patients undergoing surgery for ICC.

The metro-ticket concept was first proposed by Mazzaferro et al[11] in an attempt to predict long-term outcomes of patients undergoing liver transplantation for HCC. This prognostic tool has been demonstrated to stratify accurately HCC patients with regard to long-term survival, as prognosis worsened with increasing tumor size and number, just as longer trips on the "metro" result in a higher "ticket" price. The system was recently updated to incorporate tumor size, number and AFP as continuous rather than dichotomous

variables, thus, providing a better prognostic stratification of patients with HCC.[12] Sasaki et al[13] recently applied the metro-ticket concept using the maximum tumor size and number of lesions to define prognosis of patients undergoing resection for CRLM. In a different study, Lu et al[14] developed a novel TNM staging system for gastric cancer based on the same principles. To date, however, no study has applied the metro-ticket concept to patients undergoing surgery for ICC. In the current study, we sought to apply these principles to predict 5-year OS among patients undergoing resection for ICC using a large multi-institutional database. Of note, among 643 patients undergoing surgery for ICC, 5-year OS was 42.7%. When patients were divided to groups according to their predictive 5-year OS, actual survival was similar to the OS predicted by the calculator. Indeed, patients with predicted 5-year OS of <25%, 26%-50%, 51%-75%, and >75% had an actual 5-year OS of 12.9%, 40.8%, 59.0%, and 70.5%, respectively (Figure 2). In contrast to previous studies, which have included only two or three factors in the prediction of OS,[10,26] our calculator assigned weights to each of the variables included in the multivariable model. Indeed, previous multi-institutional and registry analyses have demonstrated that except for tumor size and number,[33-37] other factors such as CA19-9 levels, margin, and lymph node status as well as major and microscopic vascular invasion are important determinants of long-term outcomes, and, thus, should be taken into account when predicting the OS of patients with ICC.[38-44] As such, our calculator could provide a more accurate prediction of long-term outcomes for patients undergoing surgery for ICC.

Recently, there has been a growing interest in the accessibility and utilization of online calculators by both health care providers and patients to find information about health promotion and disease management.[45-47] Of note, cancer prognosis is among the leading topics of information that is sought by both physicians and patients.[47] Indeed, Rabin et al[47] recently performed a systematic review and noted that the prognostic calculators have been increasingly utilized by physicians and patients with prostate, colorectal, breast cancer, and melanoma. Online prediction tools are particularly relevant in settings where prognosis of patients can be heterogeneous and dependent on a range of factors such as in ICC. To this end, an easy-to-use web-based calculator was created that was able to predict the prognosis of patients undergoing surgery for ICC. Importantly, by providing information on tumor characteristics (ie, size, number, and differentiation), tumor marker (ie, CA19-9), and histopathological findings (ie, margin and lymph node status, microvascular invasion), the calculator estimated the 5-year survival probability (Figure 1). Of note, the predictive ability of this model was good in both the training (C-statistic = 0.696) and validation cohorts (C-statistic = 0.672), suggesting that this calculator may be a useful tool for surgeons treating patients with ICC. In particular, accurate data to risk stratify patients may help identify which patients may benefit the most from adjuvant therapy.[48,49]

The current study had several limitations that should be considered when interpreting the results. As with all retrospective studies, selection bias may have influenced which patients were offered surgery. In addition, data used in the prediction model were largely obtained based on the postoperative factors and thus the calculator would be largely applicable in estimating long-term prognosis following surgery. Finally, information on the response to neoadjuvant therapy and its potential impact on survival was not included in the model.

In conclusion, long-term outcomes of patients undergoing curative-intent resection for ICC were relatively poor with a 5-year OS of approximately 40%. Prognosis of patients was associated with factors such as tumor size and number, serum CA19-9 levels, lymph node status, margin status, and tumor differentiation, major and microscopic vascular invasion as well as receipt of adjuvant chemotherapy. On the basis of these factors, a novel, easy-to-use online calculator was developed to estimate the 5-year survival probability for patients undergoing resection for ICC. This "metro-ticket" calculator was able to accurately predict the actual survival of patients and performed well on internal validation. This tool could help provide clinicians useful information to guide treatment decision-making and help inform conversations about prognosis with patients after surgical resection of ICC.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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